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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,900	01/24/2006	Dominique P. Bridon	C2077-7016US	6100

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
10/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/565,900	BRIDON ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-131* is/are pending in the application.

4a) Of the above claim(s) *126-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-125 and 131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/11/08, 6/25/08, 6/25/08, 1/21/08,1/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 38-131 are pending. Election of Group I, claims 38-125 and 131, was made **without** traverse in the reply filed on 07/11/2008. Claims 126-130 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. In addition, Applicant elected the insulin species native human insulin (formula I), the position species the N-terminus of chain B and the linker species $NH_2(CH_2)_nCOOH$ wherein n is 1-20. A prior art rejection is made on these species therefore the search was not extended to additional species. However, the prior art utilized in the rejection reads on all additional insulin and position species and therefore the election of species with respect to insulin and position of coupling is withdrawn. The prior art utilized also reads on the linker AEEA-AEEA. The search for linkers was not further extended.

3. In summary, claims 38-131 are pending; claims 126-130 are withdrawn, and claims 38-125 and 131 are examined.

Specification

4. The use of the trademarks Lantus, Levemir, Humalog, Novolog, Apidra, Biotage, Prism, One Touch Ultra, DAC and CD has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 38-41, 48, 49, 64, 65 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu *et al.* (*Biochemistry*, **1979**, *18*, 690-7). Liu *et al.* teach *m*-maleidobenzoylinsulin (MB-insulin, p. 691, col. 2). MB-insulin was synthesized through the reaction of porcine insulin with *m*-maleidobenzoyl-*N*-hydroxysuccinimide ester (MS). The hydroxysuccinimide group reacts with free amino groups on insulin to yield insulin linked to a maleimido-containing group by a benzoyl linker (Fig. 1). Free amino acids on insulin include the N-terminal amino groups of the A and B chain and the side chain of lysine B29. Liu *et al.* does not teach that the MB-insulin can be conjugated to blood components such as albumin or recombinant albumin. Because the structure of the insulin derivative taught by Liu *et al.* is identical to the claimed derivative, the prior of Liu *et al.* inherently meets this functional limitation. With respect to claim 16, the MB-insulin was purified in phosphate buffered saline which is a pharmaceutically acceptable carrier.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 38-125 and 131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008) in view of Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717).

9. Bridon *et al.* (WO 00/69900) teach therapeutic peptides conjugated to protein carriers such as albumin (p. 3, ln29-30). Bridon *et al.* teach that maleimide derivatives of therapeutic peptides may be prepared by reacting the peptide with maleimidopropionic acid (MPA). The MPA will react with free amines at the N-terminus or lysine side chain. (p. 73, lns. 1-14) Bridon *et al.* teaches methods of modifying peptide containing multiple cysteines with MPA at the N-terminus (example 65) and at an internal lysine (example 67). Bridon *et al.* teaches that insulin (p. 26) is an example of a therapeutic peptide that can be modified with an maleimido-containing group and subsequently conjugated to albumin.

10. Bridon *et al.* (WO 00/69900) does not explicitly recite the synthesis of the insulin derivative or conjugate.

11. Jones *et al.* teach an insulin analogue comprising insulin covalently linked to a pendant molecular group which has an affinity for one or more binding proteins present in the human or animal circulatory system to treat glycemic diseases (p. 7, lns. 1-4). The exemplified analogue comprises thyroxine conjugated to the B1 residue (pp. 15-17). Thyroxine binds non-covalently to several proteins in human circulatory system including thyroxine binding globulin, thyroxine binding prealbumin and albumin (p. 10, lns. 24-27). The insulin analogue may be injected to the blood stream where it will come into contact with the binding protein for which the pendant group has an affinity. Thus, the insulin analogue will become non-covalently bound to the blood protein and will have increased stability in the bloodstream of the patient (p. 7, lns. 5-27). Jones *et al.* differs from the instant claims in that the complex between insulin and the blood protein is non-covalent.

12. Jonassen *et al.* teach the acylation of insulin at the B29 position by fatty acids allowing binding to serum albumin (Table 1) and it use in the treatment of diabetes (p. 676).

13. Baudys *et al.* teaches an insulin conjugate comprising carboxymethyl dextan attached to the A1 position that exhibits prolonged insulin action.

14. Bridon *et al.* (CA 2363712) teach modified insulinotropic peptides conjugated to MPA at free lysines directly or via a AEEA linker, that are capable of reacting with albumin in the blood stream (p. 3, lns. 1-9).

15. Vajo *et al.* teach native human insulin (formula I) and the analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes (abstract).

16. It would have been obvious to one of ordinary skill in the art to apply the method for the coupling of therapeutic peptides to the reactive moiety maleimidopropionic acid taught by Bridon *et al.* (WO 00/69900 and CA 2363712) to insulin and to use the resulting MPA-derivitized insulin to react with the blood protein albumin to form a stable insulin-albumin covalent complex according to the method of albumin conjugation taught by Bridon *et al.*. (WO 00/69900 and CA 2363712). The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based on the MPA reaction chemistry taught by Bridon *et al.* (WO 00/69900) and Bridon *et al.* (CA 2363712) and the insulin conjugation chemistry taught by Jones *et* al (B1 conjugation), Jonassen *et al.*(B29 conjugation), and Baudys *et al.* (A1 conjugation). The reactive group MPA comprises the maleimido moiety and the linker aminopriopionic acid. It would have been obvious to use any insulin such as native human insulin or the analogs taught by Vajo *et al.* These teachings satisfy all of the limitations of claims 38-55, 60-61, 64, 66-83, 88, 89, 92, 94, 96, 98, 100, 102, and 112. The skilled artisan would have been motivated to do so based on the suggestion of Bridon *et al.* that insulin is a suitable peptide for the method. The skilled artisan would have been further motivated to do so based on the teachings in the prior art of Jonassen *et al.* and Baudys *et al.* demonstrating the benefit of binding insulin to blood proteins such as albumin in order to increase stability of the molecule. There would have been a reasonable expectation of success given the conjugation chemistry taught in the references of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.* and Bridon *et al.* (CA 2363712) which show that it is possible to conjugate MPA to free

amines at the N-terminus and an internal lysine of a peptide in general and that it is possible to modify the free amines of A1, B1 and lysine B29 in insulin, specifically.

17. With respect to claims 52-55 and 80-83, it would have also been obvious to use the linker AEEA-AEEA taught by Bridon *et al.* (CA 2363712). With respect to claims 116-125, it is obvious to use insulin to treat diabetes. With respect to claims 124 and 125, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* or *ex vivo* (p. 40, lns. 17-28). For *ex vivo* covalent bond formation, Bridon *et al.* teach that the MPA-derivatized therapeutic peptide is added to a saline solution containing human serum albumin to permit covalent bond formation between the derivatized peptide and the blood component. Once the derivatized peptide has reacted with the blood component to form a peptide-protein conjugate, Bridon *et al.* teach that the conjugate may be administered to the patient, satisfying the limitations of claims 117, 121-123 and 125. For *ex vivo* formation, it would be obvious to use recombinant human serum albumin, satisfying claims 65, 93, 95, 97, 99, 101, 103 and 113. Alternatively, Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. With respect to claims 56-59, 62, 63, 84-87, 90, 91, 104-111, 114 and 115, it would have been obvious to vary the length of the alkyl chain in MPA to optimize the linker length through routine experimentation in view of Bridon *et al.* (CA 2363712, p. 5). With respect to claim 131, Bridon *et al.* teaches that the BOC protecting group ay be utilized (p. 6).

18. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 38-41, 43-69, 71-117 and 131 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 26 of copending application 11/112,277. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 26 of copending application 11/112,277 recites insulin derivatives comprising an insulin molecule and a reactive maleimido-containing group for covalently bonding a blood protein, and conjugates of said insulin derivatives and the blood protein albumin. The species recited in claim 26 of copending application 11/112,277 include: insulin B1-MPA, insulin A1-MPA, insulin B1-OA-MPA, insulin B29-MPA, insulin B29-AEES2-MPA, insulin B1-AEES2-MPA, and insulin B29-OA-MPA, wherein A1, B1 and B29 refer to the amino acid to which the maleimido-containing group is linked, MPA is maleimidopropionic acid, OA is octanoic acid, AEES is amino ethoxy ethyl amino succinic acid

and insulin is native human insulin identical to instantly claimed formula I. The albumin may be serum or recombinant (claim 6). The insulin derivatives and albumin-conjugates recited in claim 26 anticipate the instant claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 42 and 70 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 26 of copending application 11/112,277 as applied to claims 38-41, 43-69, 71-117 and 131 above, in further view of Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Vajo *et al.* teach native human insulin (formula I) and the analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes (abstract). It would have been obvious to use any of the insulins analogs taught by Vajo *et al.* to form the insulin conjugates and derivatives claimed in copending application 11/112,277. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 118-125 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 26 of copending application 11/112,277 as applied to claims 38-41, 43-69, 71-117 and 131 above, in further view of Bridon *et al.* (CA 2363712). Bridon *et al.* teach modified insulinotropic peptides conjugated to MPA at free lysines directly or via a AEEA linker, that are capable of reacting with albumin in the blood stream (p. 3, lns. 1-9). This method is identical to that used to form the insulin derivatives and conjugates in copending application 11/112,277. With respect to claims 124 and 125, Bridon *et*

al. (CA 2363712) teach that the conjugation method can be performed *in vivo* or *ex vivo* (p. 40, lns. 17-28). For *ex vivo* covalent bond formation, Bridon *et al.* teach that the MPA-derivatized therapeutic peptide is added to a saline solution containing human serum albumin to permit covalent bond formation between the derivatized peptide and the blood component. Once the derivatized peptide has reacted with the blood component to form a peptide-protein conjugate, Bridon *et al.* teach that the conjugate may be administered to the patient, satisfying the limitations of claims 117, 121-123 and 125. For *ex vivo* formation, it would be obvious to use recombinant human serum albumin, satisfying claims 65, 93, 95, 97, 99, 101, 103 and 113. Alternatively, Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. It would have been obvious to use the insulin derivatives and conjugates claimed in copending application 11/112,277 in the methods of administering taught by Bridon *et al.* to treat diabetes. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claims 38-41, 43-69, 71-117 and 131 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 44 of copending application 11/981,474. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 44 of copending application 11/981,474 recites insulin derivatives comprising an insulin molecule and a reactive maleimido-containing group for covalently bonding a blood protein, and conjugates of said insulin derivatives and the blood

protein albumin. The species recited in claim 44 of copending application 11/981,474include: insulin B1-MPA, insulin A1-MPA, insulin B1-OA-MPA, insulin B29-MPA, insulin B29-AEES2-MPA, insulin B1-AEES2-MPA, and insulin B29-OA-MPA, wherein A1, B1 and B29 refer to the amino acid to which the maleimido-containing group is linked, MPA is maleimidopropionic acid, OA is octanoic acid, AEES is amino ethoxy ethyl amino succinic acid and insulin is native human insulin identical to instantly claimed formula I. The albumin may be serum or recombinant (claim 45). The insulin derivatives and albumin-conjugates recited in claim 26 anticipate the instant claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 42 and 70 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 44 of copending application 11/981,474 as applied to claims 38-41, 43-69, 71-117 and 131 above, in further view of Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Vajo *et al.* teach native human insulin (formula I) and the analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes (abstract). It would have been obvious to use any of the insulins analogs taught by Vajo *et al.* to form the insulin conjugates and derivatives claimed in copending application 11/981,474. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 118-125 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 44 of copending application 11/981,474

as applied to claims 38-41, 43-69, 71-117 and 131 above, in further view of Bridon *et al.* (CA 2363712). Bridon *et al.* teach modified insulinotropic peptides conjugated to MPA at free lysines directly or via a AEEA linker, that are capable of reacting with albumin in the blood stream (p. 3, lns. 1-9). This method is identical to that used to form the insulin derivatives and conjugates in copending application 11/981,474. With respect to claims 124 and 125, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* or *ex vivo* (p. 40, lns. 17-28). For *ex vivo* covalent bond formation, Bridon *et al.* teach that the MPA-derivatized therapeutic peptide is added to a saline solution containing human serum albumin to permit covalent bond formation between the derivatized peptide and the blood component. Once the derivatized peptide has reacted with the blood component to form a peptide-protein conjugate, Bridon *et al.* teach that the conjugate may be administered to the patient, satisfying the limitations of claims 117, 121-123 and 125. For *ex vivo* formation, it would be obvious to use recombinant human serum albumin, satisfying claims 65, 93, 95, 97, 99, 101, 103 and 113. Alternatively, Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. It would have been obvious to use the insulin derivatives and conjugates claimed in copending application 11/981,474 in the methods of administering taught by Bridon *et al.* to treat diabetes. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 38-125 and 131 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-49 of copending application 11/982,033, in view of Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008), Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Although the conflicting claims are not identical, they are not patentably distinct from each other.

27. Claim 27 of copending application 11/982,033 recites a modified peptide comprising a maleimido-containing reactive group coupled optionally via a linker to the peptide that is capable of covalently binding *in vivo* or *in vitro* a blood component albumin, wherein the genus of peptides includes insulin. Claim 37 of copending application 11/982,033 recites the modified peptide conjugated to the blood component albumin, wherein the genus of peptides includes insulin. Claims 30-35 of copending application 11/982,033 recite the reactive group maleimidopropionic acid (MPA) and poly ethoxy amino acid linkers. Claim 39 recites a pharmaceutical composition comprising the modified peptide. Claims 48 and 49 recite a method of treating a disorder by administering the modified peptide or the conjugate, respectively.

28. There are no claims in copending application 11/982,033 drawn specifically to the species insulin.

29. The teachings of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.*, Bridon *et al.* (CA 2363712) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717) are described above.

30. It would have been obvious to select insulin from the genus of peptides recited in the claims of copending application 11/982,033and to form the MPA-modified insulin and subsequently the insulin conjugated to albumin. It would have been further obvious to use the MPA-modified insulin or the insulin-albumin conjugate to treat diabetes. The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based on the MPA reaction chemistry taught by Bridon *et al.* (WO 00/69900) and Bridon *et al.* (CA 2363712) and the insulin conjugation chemistry taught by Jones *et* al (B1 conjugation), Jonassen *et al.*(B29 conjugation), and Baudys *et al.* (A1 conjugation). The reactive group MPA comprises the maleimido moiety and the linker aminopriopionic acid. It would have been obvious to use any insulin such as native human insulin or the analogs taught by Vajo *et al.* These teachings satisfy all of the limitations of claims 38-55, 60-61, 64, 66-83, 88, 89, 92, 94, 96, 98, 100, 102, and 112. The skilled artisan would have been motivated to do so based on the teachings in the prior art of Jonassen *et al.* and Baudys *et al.* demonstrating the benefit of binding insulin to blood proteins such as albumin in order to increase stability of the molecule. There would have been a reasonable expectation of success given the conjugation chemistry taught in the references of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.* and Bridon *et al.* (CA 2363712) which show that it is possible to conjugate MPA to free amines at

the N-terminus and an internal lysine of a peptide in general and that it is possible to modify the free amines of A1, B1 and lysine B29 in insulin, specifically.

31. With respect to claims 52-55 and 80-83, it would have also been obvious to use the linker AEEA-AEEA taught by Bridon *et al.* (CA 2363712). With respect to claims 116-125, it is obvious to use insulin to treat diabetes. With respect to claims 124 and 125, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* or *ex vivo* (p. 40, lns. 17-28). For *ex vivo* covalent bond formation, Bridon *et al.* teach that the MPA-derivatized therapeutic peptide is added to a saline solution containing human serum albumin to permit covalent bond formation between the derivatized peptide and the blood component. Once the derivatized peptide has reacted with the blood component to form a peptide-protein conjugate, Bridon *et al.* teach that the conjugate may be administered to the patient, satisfying the limitations of claims 117, 121-123 and 125. For *ex vivo* formation, it would be obvious to use recombinant human serum albumin, satisfying claims 65, 93, 95, 97, 99, 101, 103 and 113. Alternatively, Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. With respect to claims 56-59, 62, 63, 84-87, 90, 91, 104-111, 114 and 115, it would have been obvious to vary the length of the alkyl chain in MPA to optimize the linker length through routine experimentation in view of Bridon *et al.* (CA 2363712, p. 5). With respect to claim 131, Bridon *et al.* teaches that the BOC protecting group ay be utilized (p. 6).

32. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

33. Claims 38--125 and 131 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-58 of copending application 11/645,297, in view of Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008), Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Although the conflicting claims are not identical, they are not patentably distinct from each other.

34. Claim 8 of copending application 11/645,297 recites a conjugate comprising albumin covalently linked to a compound, wherein the conjugate is formed in solution by contacting albumin with a compound comprising a reactive group. Claim 34 recites the reactive group MPA. Claim 27 recites a genus of compounds including insulin.

35. There are no claims in copending application 11/645,297 drawn specifically to the species insulin.

36. The teachings of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.*, Bridon *et al.* (CA 2363712) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717) are described above.

37. It would have been obvious to select insulin from the genus of compounds recited in the claims of copending application 11/645,297 and to form the MPA-modified insulin and

subsequently the insulin conjugated to albumin. It would have been further obvious to use the MPA-modified insulin or the insulin-albumin conjugate to treat diabetes. The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based on the MPA reaction chemistry taught by Bridon *et al.* (WO 00/69900) and Bridon *et al.* (CA 2363712) and the insulin conjugation chemistry taught by Jones *et* al (B1 conjugation), Jonassen *et al.*(B29 conjugation), and Baudys *et al.* (A1 conjugation). The reactive group MPA comprises the maleimido moiety and the linker aminopriopionic acid. It would have been obvious to use any insulin such as native human insulin or the analogs taught by Vajo *et al.* These teachings satisfy all of the limitations of claims 38-55, 60-61, 64, 66-83, 88, 89, 92, 94, 96, 98, 100, 102, and 112. The skilled artisan would have been motivated to do so based on the teachings in the prior art of Jonassen *et al.* and Baudys *et al.* demonstrating the benefit of binding insulin to blood proteins such as albumin in order to increase stability of the molecule. There would have been a reasonable expectation of success given the conjugation chemistry taught in the references of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.* and Bridon *et al.* (CA 2363712) which show that it is possible to conjugate MPA to free amines at the N-terminus and an internal lysine of a peptide in general and that it is possible to modify the free amines of A1, B1 and lysine B29 in insulin, specifically.

38. With respect to claims 52-55 and 80-83, it would have also been obvious to use the linker AEEA-AEEA taught by Bridon *et al.* (CA 2363712). With respect to claims 116-125, it is obvious to use insulin to treat diabetes. With respect to claims 124 and 125, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* or *ex vivo* (p. 40, lns. 17-

28). For *ex vivo* covalent bond formation, Bridon *et al.* teach that the MPA-derivatized therapeutic peptide is added to a saline solution containing human serum albumin to permit covalent bond formation between the derivatized peptide and the blood component. Once the derivatized peptide has reacted with the blood component to form a peptide-protein conjugate, Bridon *et al.* teach that the conjugate may be administered to the patient, satisfying the limitations of claims 117, 121-123 and 125. For *ex vivo* formation, it would be obvious to use recombinant human serum albumin, satisfying claims 65, 93, 95, 97, 99, 101, 103 and 113. Alternatively, Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. With respect to claims 56-59, 62, 63, 84-87, 90, 91, 104-111, 114 and 115, it would have been obvious to vary the length of the alkyl chain in MPA to optimize the linker length through routine experimentation in view of Bridon *et al.* (CA 2363712, p. 5). With respect to claim 131, Bridon *et al.* teaches that the BOC protecting group ay be utilized (p. 6).

39. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

40. No claims are allowed.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

42. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

43. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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cmb